University of Cambridge
Division of Transfusion Medicine

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Our ref: LMW/cmh/SACBC.**L237**

Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane, rm 1061,
Rockville, MD 20852
USA

Fax: 001 301 827 6870

Dear Sir/Madam

Gamma Irradiation of Blood Components: A Pilot Programme for Licensing Draft Guidance

This document was considered by the Standing Advisory Committee on Blood Components, which is part of the UK Transfusion Services Guidelines structure. We found it a very helpful document and broadly in line with our own guidelines, although there are some differences:

(1) **Dosage**
We have specified 25 Gy to all parts of the pack, as we have been made aware of cases in the literature of occasional failure of protection at lower doses. With most irradiators, a field can be designed such that no part receives >40 Gy.

(2) **Indicators**
We require a radiation-sensitive label on every pack, which is found to be very helpful by hospital staff administering the component.

(3) **Dating Period**
When we derived the UK Guidelines we felt that the aggregate period between collection and outdate should not be more than 28 days. We, therefore, allow irradiation of red cell units up to 14 days from collection, with a further 14 day storage thereafter. However, we would not permit 28 day storage after irradiation as a blanket recommendation.

(4) **Temperature During Irradiation**
We do not currently validate this and your document has made us consider whether this should become a recommendation.

I realise these comments may have reached you after the closing date for comment, but hope that they may still be of value.

Yours faithfully

Lorna Williamson

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Consultant / University Lecturer in Transfusion Medicine

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that registration would be required, even though the product is not offered for commercial distribution in the U.S. We respectfully disagree with this conclusion.

1. There is no statutory requirement that foreign establishments register with FDA if the imported products are not marketed in the U.S.

FDAMA amended section 510(i) of the Federal Food, Drug, and Cosmetic Act (FDC Act) to read, in part:

> (1) Any establishment within any foreign country engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or device that is imported or offered for import into the United States shall register with the Secretary the name and place of business of the establishment and the name of the United States agent for the establishment.
>
> (2) The establishment shall also provide the information required by subsection (j).

21 U.S.C. § 360(i)(1)-(2).

Section 510(i) does not expressly state, "imported or offered for import into the United States for commercial distribution"; rather, the section is silent on this point. However, section 510(j), referenced in new section 510(i)(2), suggests that only firms which manufacture, prepare, propagate, compound, or process products for commercial distribution must register. Specifically, according to section 510(j), companies that perform the aforementioned activities "for commercial distribution" must list their products with FDA. 21 U.S.C. § 360(j). That is, a product which is sold in the U.S. must be listed and the facility that manufactured that product must be registered; if a product is not sold here, listing and registration are not required. For example, a foreign company might export a product into a U.S. FTZ without marketing it in the U.S. In this type of case, the FDC Act suggests that the foreign establishment should not be required to register with FDA. This interpretation is consistent with the Congressional intent underlying the passage of FDAMA, which, in part, was to reduce administrative burdens on industry and FDA. The interpretation is also consistent with the common understanding that the FDC Act should appropriately ensure the safety and effectiveness of drugs and devices of foreign origin that will be commercially distributed in the U.S. but need not extend beyond this purpose.

2. FDA should defer to the regulatory authorities in the exporting or destination country to determine whether a foreign establishment must register when the product is imported into, but is not commercially distributed in, the U.S.

FDA clearly has jurisdiction over companies that manufacture products sold in the U.S. However, when the imported products are not sold or manufactured in the U.S. but, rather, are exported to another country, FDA's control over these firms should be limited. For example, a company in France ships a product to a U.S. FTZ for holding before it is exported to Japan. The product is not sold in the U.S. and nothing is done to the product here (e.g., no changes to specifications). In this case, the regulatory authorities in France or Japan, or both, might require the company to register its establishment so that the appropriate government agency might monitor and inspect the manufacturing facility. However, registration with FDA would not be justified, because the product will neither be produced nor sold in the U.S. Therefore, in a scenario where a product is imported but is not commercially distributed in the U.S., FDA should defer to the regulatory authorities in the exporting or destination country, or both, to establish a registration procedure, if appropriate.

3. There is no reason for FDA to require foreign establishments to register that merely import products into the U.S., but which do not market these products in the U.S.

In addition to the aforementioned reasons, FDA should not require the registration of foreign establishments that do not market their products in the U.S. because it is simply not necessary. As previously noted, the exporting and destination countries can impose their own registration requirements on foreign manufacturers that do business in their territories. Moreover, under section 510(i)(3), the Secretary of Health and Human Services (and, presumably by delegation, FDA) is authorized

> to enter into cooperative arrangements with officials of foreign countries to ensure that adequate and effective means are available for purposes of determining, from time to time, whether drugs or devices manufactured, prepared, propagated, compounded, or processed by an establishment described in paragraph (1) [i.e., the type of foreign establishment described above], if imported or offered for import into the United States, shall be refused admission on any of the grounds set forth in section 801(a) [of the FDC Act].

21 U.S.C. § 360(i)(3). That is, the FDC Act provides that FDA may work with other countries to control the importation of products, presumably for commercial distribution in the U.S.

There are regulatory safeguards already in place to provide that a foreign establishment must register with the appropriate regulatory authorities if its products are commercially distributed in those countries, including the U.S. Because these protections exist, any attempt by FDA to require foreign establishments to register here even if they do not sell products in the U.S. is not necessary. Such a requirement would only impose an additional administrative burden on industry and FDA without providing a significant countervailing benefit, which is contrary to what Congress intended when it enacted FDAMA. Of course, if an imported good enters commercial distribution in the U.S. and the firm is not registered with the Agency, FDA has the authority to take appropriate action.

* * * * *

In conclusion, we respectfully request that FDA clarify, whether in the Preamble to the Final Rule or in the final regulation itself, that foreign establishments are not required to register with FDA if the imported products are not introduced for commercial distribution in the U.S.

We appreciate the opportunity to submit these comments to FDA's proposed rule. Please feel free to contact me at (404) 873-8690 if you have any questions.

Sincerely,

Alan G. Minsk

AGM/mkm

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bcc: Dave Jespersen

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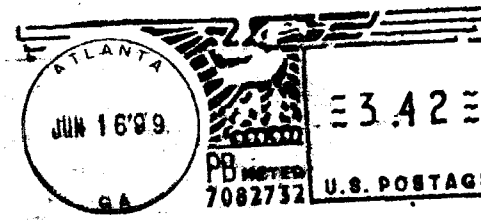

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